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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/000,213	11/14/2001	Brenda F. Baker	RTS-0327	1275

7590 12/16/2003

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/000,213	BAKER ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9 and 11-29* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,11-18 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks, filed September 12, 2003.

Claims 1, 2, 4-9, and 11-16 have been amended. Claims 19 and 20 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. New claims 21-29 are acknowledged.

Claims 1, 2, 4-9, 11-28, and 21-29 are pending in the instant application.

Information Disclosure Statement

The Information Disclosure Statement, filed September 12, ~~2203~~ 2003 to include the English translation of the WO 01/38393 is acknowledged. KAL 12-10-03

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 11, 12 and 13 were rejected under 35 U.S.C. 112, second paragraph for being indefinite. **This rejection is withdrawn** in view of Applicants amendment to the claims to replace the term "compound" with the term "an oligonucleotide", filed September 12, 2003.

Claims 15-18 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the expression of vitamin D

nuclear receptor in cells (*in vitro*) using an oligonucleotide 8 to 50 nucleotides in length that targets and inhibits the expression of vitamin D nuclear receptor, does not reasonably provide enablement for a method of inhibiting the expression of vitamin D nuclear receptor in cells (*in vivo*) or method of treating human having a disease or condition associated with vitamin D nuclear receptor using any compound 8 to 50 nucleotides in length that targets and inhibits the expression of vitamin D nuclear receptor. **This rejection is maintained** for the reasons of record set forth in the previous Office Action, filed March 12, 2003.

Applicants argue that there is no evidence of record indicating that a skilled artisan would be unable to practice the methods as claimed. Applicants argue that the Examiner falls short of demonstrating that the compounds recited in the claims would not be expected to exhibit at least some level of activity. Applicants argue that the rejection appears to be resurrecting a stringent requirement of therapeutic utility that was unambiguously rejected by the USPTO many years ago. Applicants direct the Examiner to §M.P.E.P. 2107.02. Applicants argue the enablement requires only that the application teach how to make and use the invention without undue experimentation.

This is not found persuasive because the issue at hand is not whether the compounds recited in the claims would not be expected to exhibit at least some level of activity, but instead whether the instant application teaches how to make and use the invention without undue experimentation. The Examiner has provided several arguments to show that the disclosure fails to teach the skilled artisan how to make and use the invention without undue experimentation. See for example, page 7, last paragraph, where it states, "the instant specification does not show any specific link between vitamin D nuclear receptor and any specific disease or condition such

that treatment with vitamin D nuclear receptor antisense would be an apparent treatment option. It is unclear how the specific cell culture (*in vitro*) data is correlated with/or representative of treatment to wide range of diseases or conditions (*in vivo*) with any vitamin D nuclear receptor antisense".

Applicants have directed the Examiner to §M.P.E.P. 2107.02, but it is unclear how this reference is related to the rejection at hand since §M.P.E.P. 2107.02 is related to rejections for lack of utility. The rejection of record is not for lack of utility, but is instead for scope of enablement.

Applicants argue that the instant specification teaches a claimed method of inhibiting the expression of vitamin D receptor in cells or tissues by demonstrating that effective antisense oligonucleotides inhibit human vitamin D receptor mRNA levels in a cellular assay. Applicants contend that the results from the cellular assay provides sufficient data to predict that a claimed method of treating an animal having a disease or condition associated with vitamin D nuclear receptor will provide some level of inhibition of mRNA levels.

This is not found persuasive because as discussed in the previous Office Action, it is not yet clear whether *in vitro* screening techniques will identify ODN's that are effective *in vivo* (see Branch, Jen et al. and Dias et al.). Therefore, because of the unpredictability of the art and the specification's lack of particular guidance or particular direction, the quantity of experimentation required of one of skill in the art would include the de novo determination of how to engineer and deliver an antisense targeting vitamin D nuclear receptor such that any disease or condition (e.g. a cancer or a developmental disorder) associated thereto would be treated to any degree.

Therefore, undue experimentation would be required of one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102

Claims 1, 2, 4, 5, 11 and 15 were rejected under 35 USC 102(b) as being anticipated by Hmama et al. (Journal of Experimental Medicine, 1999 Vol. 190:1583-1594). **This rejection is withdrawn** in view of Applicants Amendment to the claims to include an oligonucleotide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor; wherein said compound specifically hybridizes with said nucleic acid molecule encoding vitamin D nuclear receptor and inhibits the expression of vitamin D nuclear receptor, and wherein the oligonucleotide is a chimeric oligonucleotide.

Claim Rejections - 35 USC § 103

Claims 1, 6-10 and 12-14 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hmama et al. (Journal of Experimental Medicine, 1999 Vol. 190:1583-1594) in view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). **This rejection is withdrawn in view of the new grounds of rejection presented below.**

Claims 1, 2, 4-9, and 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hmama et al. (Journal of Experimental Medicine, 1999 Vol. 190:1583-1594) in view of

Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claim 1 is drawn to an oligonucleotide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor; wherein said compound specifically hybridizes with said nucleic acid molecule encoding vitamin D nuclear receptor and inhibits the expression of vitamin D nuclear receptor, and wherein the oligonucleotide is a chimeric oligonucleotide. Claims 2, 4-9, and 11-15 depend from claim 1 and include all the limitations of claim 1, with the further limitations, wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claims 12-14 are drawn to a composition comprising an oligonucleotide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor; wherein said compound specifically hybridizes with said nucleic acid molecule encoding vitamin D nuclear receptor and inhibits the expression of vitamin D nuclear receptor, and wherein the oligonucleotide is a chimeric oligonucleotide and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system. Claim 15 is drawn to a method of inhibiting the expression of vitamin D nuclear receptor in cells or tissues comprising contacting the cells or tissues with an oligonucleotide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor; wherein the oligonucleotide is a chimeric oligonucleotide.

Hmama et al. teach a 21-base paired phosphorothioate antisense oligonucleotide targeting the start codon of the human vitamin D nuclear receptor (see page 1585, sense and antisense oligonucleotides). Hmama et al. also teach that the antisense oligonucleotide was expressed in THP-1 cells and inhibited vitamin D nuclear receptor protein expression (see Figure 6A). Hmama et al. further teach that vitamin D nuclear receptor is required for D_3-iunduced expression of CD14 mRNA and thus vitamin D nuclear receptor signaling has a novel role in myeloid cell differentiation.

Hmama et al. do not teach the oligonucleotide is a chimeric oligonucleotide; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; and a composition comprising the oligonucleotide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Baracchini et al. teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Baracchini et al. further teach antisense oligonucleotides with phosphorothioate-modified backbones (see column 6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19)

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to modify the antisense nucleic acids targeting vitamin D nuclear receptor taught by Hmama et al. with various modifications and substitutions such as a modified internucleoside linkage, a modified sugar moiety, a 2'-O-methoxyethyl sugar moiety, a modified nucleobase, a 5-methylcytosine, a chimeric oligonucleotide and a composition comprising an oligonucleotide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system, following the methods of Baracchini et al. and Fritz et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to modify the antisense oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological experiments (see Baracchini et al., column 3, lines 17-41, column 6, line 37 and Table I and Fritz et al. page 287, last paragraph).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hmama et al. (Journal of Experimental Medicine, 1999 Vol. 190:1583-1594) in view of Cowsert, L. [U.S. Patent No. 6,566,133].

Claim 21 is drawn to an oligonucleotide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor; wherein said compound specifically hybridizes with said nucleic acid molecule encoding vitamin D nuclear receptor and inhibits the expression of vitamin D nuclear receptor, and wherein the oligonucleotide is a chimeric oligonucleotide, wherein the chimeric oligonucleotide comprises a composite structure of two or more oligonucleotides, selected from oligoribonucleotides, oligodeoxynucleotides, modified oligonucleotides, oligonucleosides or oligonucleotide mimetics. Claims 22-29 depend from claim 21 and includes all the limitations of claim 21, with the further limitations, wherein the chimeric oligonucleotide comprises at least one modified internucleotide linkage, one modified sugar moiety, one modified nucleobase, one ribonucleotide and at least one deoxyribonucleotide, and wherein the chimeric oligonucleotide comprises a central region of 2'-deoxynucleotides, a 5'-flanking region of 2'-O-methyoxyethyl (2'-MOE) nucleotides, and a 3'-flanking region of 2'-O-methoxyethyl (2'-MOE) nucleotides.

Hmama et al. teach a 21-base paired phosphorothioate antisense oligonucleotide targeting the start codon of the human vitamin D nuclear receptor (see page 1585, sense and antisense oligonucleotides). Hmama et al. also teach that the antisense oligonucleotide was expressed in THP-1 cells and inhibited vitamin D nuclear receptor protein expression (see Figure 6A). Hmama et al. further teach that vitamin D nuclear receptor is required for D_3-iunduced

expression of CD14 mRNA and thus vitamin D nuclear receptor signaling has a novel role in myeloid cell differentiation.

Hmama et al. do not teach the oligonucleotide is a chimeric oligonucleotide; wherein the chimeric oligonucleotide comprises a composite structure of two or more oligonucleotides, selected from oligoribonucleotides, oligodeoxynucleotides, modified oligonucleotides, oligonucleosides or oligonucleotide mimetics. Claims 22-29 depend from claim 21 and includes all the limitations of claim 21, with the further limitations, wherein the chimeric oligonucleotide comprises at least one modified internucleotide linkage, one modified sugar moiety, one modified nucleobase, one ribonucleotide and at least one deoxyribonucleotide, and wherein the chimeric oligonucleotide comprises a central region of 2'-deoxynucleotides, a 5'-flanking region of 2'-O-methyoxyethyl (2'-MOE) nucleotides, and a 3'-flanking region of 2'-O-methoxyethyl (2'-MOE) nucleotides.

Cowsert, L. teach chimeric antisense compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Such compounds have also been referred to in the art as hybrids or gapmers (see column 11, lines 63-67 and column 12, line 1). Cowsert, L. further teach chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides (see Table 2).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to modify the antisense nucleic acids targeting vitamin D nuclear receptor

taught by Hmama et al. with various modifications and substitutions such chimeric oligonucleotide; wherein the chimeric oligonucleotide comprises a composite structure of two or more oligonucleotides, selected from oligoribonucleotides, oligodeoxynucleotides, modified oligonucleotides, oligonucleosides or oligonucleotide mimetics following the methods of Cowsert, L. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to modify the antisense oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases (see Cowsert, L. column 6, lines 29-33, for example).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 746-8693.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
December 8, 2003

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER